Quality assurance in rectal cancer treatment

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Chapter 8

Patients with curative resection of cT3-4 rectal cancer after preoperative radio- or radiochemotherapy: does anybody benefit from adjuvant fluorouracil-based chemotherapy? A trial of the European Organisation for Research and Treatment of Cancer Radiation Oncology Group

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ABSTRACT

Purpose

European Organisation for Research and Treatment of Cancer (EORTC) 22921 trial compared adjuvant fluorouracil-based chemotherapy (CT) to no adjuvant treatment in a 2 x 2 factorial trial with randomisation for preoperative (chemo)radiotherapy in patients with resectable T3-4 rectal cancer. The results showed no significant impact of adjuvant CT on progression-free or overall survival, although a difference seemed to emerge at approximately, respectively, 2 and 5 years after the start of preoperative treatment. We further explored the data with the aim of refining our understanding of the long-term results.

Patients and methods

Data of 785 of the 1011 randomly assigned patients whose disease was M0 at curative surgery were used. Using meta-analytic methods, we investigated the homogeneity of the effect of adjuvant CT on the time to relapse or death after surgery (disease-free survival [DFS]) and survival in patient subgroups.

Results

Although there was no statistically significant impact of adjuvant CT on DFS for the whole group ($P > 0.5$), the treatment effect differed significantly between the ypT0-2 and the ypT3-4 patients (heterogeneity $P = 0.009$): only the ypT0-2 patients seemed to benefit from adjuvant CT ($P = 0.011$). The same pattern was observed for overall survival.

Conclusion

Exploratory analyses suggest that only good-prognosis patients (ypT0-2) benefit from adjuvant CT. This could explain why, in the whole group, the progression-free and overall survival diverged only after the poor-prognosis patients (ypT3-4) had experienced treatment failure. Patients in whom no downstaging was achieved did not benefit. This also suggests that the same prognostic factors may drive both tumour sensitivity for the primary treatment and long-term clinical benefit from further adjuvant CT.

INTRODUCTION

The European Organisation for Research and Treatment of Cancer (EORTC) 22921 trial was a 2 x 2 factorial plan, four-arm, randomised trial that questioned the value of preoperative radiochemotherapy (RT-CT) versus preoperative radiotherapy (RT) alone and the value of adjuvant chemotherapy (CT) versus none with respect to overall survival and progression-free survival in patients with potentially resectable cT3-4 M0 rectal cancer.

From April 1993 to March 2003, 1011 patients were allocated to one of the following treatment arms: arm 1, preoperative RT; arm 2, preoperative RT-CT; arm 3, preoperative RT and adjuvant CT; and arm 4, preoperative RT-CT and adjuvant CT.

The main trial results were recently published with a median follow-up of 5.4 years.[1] A first analysis showed that the addition of CT to preoperative RT induced a significant increase of the downstaging rate.[2] The long-term results[1] failed to demonstrate a significant impact of CT (either before or after surgery) on progression-free or overall survival, the primary trial end-points. The 5-year overall survival rate was 63.2% in the no-adjuvant CT and 67.2% in the adjuvant CT arms ($P = 0.12$) with a hazard ratio (HR) of 0.85 for adjuvant CT (95% confidence interval (CI), 0.68-1.04). The 5-year progression-free survival rates were 52.2% and 58.2% in the no-adjuvant and adjuvant arms, respectively ($P = 0.132$; HR = 0.87; 95% CI, 0.72-1.04). However, the progression-free and overall survival curves started to diverge at approximately, respectively, 2 and 5 years after entry onto study, suggesting that a subset of patients of better prognosis who survive 2 to 5 years after the initiation of the first treatment might benefit from the adjuvant treatment in the long-term.

We now further explore the data with the aim of refining our understanding of the long-term results. For that purpose, we will focus on the group of eligible patients whose disease had not spread to distant sites before or at surgery and in whom a complete resection was performed. This subgroup should be disease free after surgery. We will then investigate whether we can identify, on the basis of baseline patient and treatment factors as well as of preoperative and surgical treatment and outcome characteristics, a subgroup of patients who benefit significantly from the adjuvant treatment in the long-term.

PATIENTS AND METHODS

Trial design

The trial design and eligibility criteria have been reported previously,[1] and we will summarise only the main features herein. Patients age up to 80 years with resectable T3 or T4 M0 (1987 International Union Against Cancer (UICC) staging) adenocarcinoma of the

rectum,[3] located within 15 cm of the anal margin, with a WHO performance status of 0 or 1, and without previous history of cancer, angina pectoris, or inflammatory disease of the ileum or colon were eligible for the trial. Disease staging was by clinical examination, rigid sigmoidoscopy, chest X-ray, and abdominopelvic computed tomography scan. Endorectal ultrasonography was optional.

The trial was approved by the medical ethics committees of all participating centres. Informed consent was obtained from all patients before random assignment. The patients were centrally randomised at the EORTC Data Centre to RT or RT-CT as preoperative treatment and to CT or nil as adjuvant treatment.

RT consisted of a 45-Gy dose delivered in 25 fractions of 1.8 Gy to the posterior pelvis.[2,4] Irradiation techniques and treatment volumes have been reported previously.[2,4] Preoperative CT was delivered in two 5-day courses during the first and fifth weeks of RT. Surgery was planned 3 to 10 weeks thereafter, and total mesorectal excision was recommended from 1999 onwards. When allocated, the four 3-week courses of adjuvant CT had to start 3 to 10 weeks after surgery. Preoperative and adjuvant CT consisted of fluorouracil (350 mg/m^2/d) and leucovorin (20 mg/m^2/d) administered as a short intravenous infusion.

The toxicity was monitored during treatment.[4] Patients were then followed at 6-month intervals for at least 5 years by clinical examination, abdominal ultrasound, and chest x-ray; coloscopy was performed annually. Recurrences were confirmed radiologically or histologically. Local recurrence was defined as a tumour regrowth within the pelvis or perineum.

Analysis set and end-points

Only the 785 eligible patients whose disease did not spread to distant sites before or at surgery and in whom a microscopically complete (R0) resection was performed are included in the analysis (77.6% of 1011). Complete resection was defined in this study as resection with negative resection margin by both macroscopic and microscopic examination. Disease-free survival (DFS) is defined as the time from the date of surgery to the first event of locoregional or distant recurrence or death resulting from any cause; or to the date of the most recent follow-up for excluded cases. This end-point corresponds to progression-free survival in the study protocol, but is counted from the date of surgery. Survival is counted from the date of surgery to the date of death resulting from any cause or the date of most recent information if alive.

Statistical methods

The analysis is exploratory. The association between classifications and outcome are assessed by log-rank test for heterogeneity and effects represented on forest plots,[5] and the distribution of time-to-event end-points is estimated by means of Kaplan-Meier.[6]

Interaction between factors and treatment effects is summarised by the interaction HR and its associated 95% CI.[7] The interaction HR represents the ratio of the treatment HR for one level of the explanatory variable to the treatment HR in the reference level of the covariate, and thus measures how much the relative treatment effect is modulated by the covariate. For grouping patients, continuous variables were dichotomised at the sample median or at published values. Adjacent levels of discrete variables with small numbers were lumped together. Two-sided tests were used with a 5% significance level. All analyses but those of the preoperative treatment were stratified for the allocated preoperative treatment.

RESULTS

A total of 226 patients were excluded from the analysis (102 initially allocated to no adjuvant CT and 124 to adjuvant CT): 15 were ineligible, 45 had metastatic progression before surgery, 57 have unknown metastatic status, 10 were not resected despite disease being M0, and 78 had an incomplete resection; in 21, the information regarding completeness of the resection was unknown.

Of the 785 patients included in the analysis, 199 had been randomly assigned to the RT arm without adjuvant CT, 204 to RT-CT arm without adjuvant CT, 190 to the RT arm with adjuvant CT, and 192 to the RT-CT arm with adjuvant CT. In the analysed set, all patients allocated adjuvant CT received at least one adjuvant CT cycle. The four adjuvant CT cycles were delivered to 140 (73.7%) of 190 patients and 142 (73.9%) of 192 patients allocated adjuvant CT in the RT and RT-CT arms, respectively.

Of the patients in the RT arm, 233 (57.8%) were alive and free of disease at a median follow-up of 5.2 years from surgery, compared with 237 (62.0%) in the RT-CT arm (Figure 1). The first relapse was locoregional in 37 patients receiving RT versus 19 patients receiving RT-CT, distant relapse occurred in 98 versus 91 patients, the two types of events occurred concurrently in five versus eight patients, a death without relapse occurred in 28 versus 25 patients, and relapse at unspecified localisation occurred in two patients in each arm.

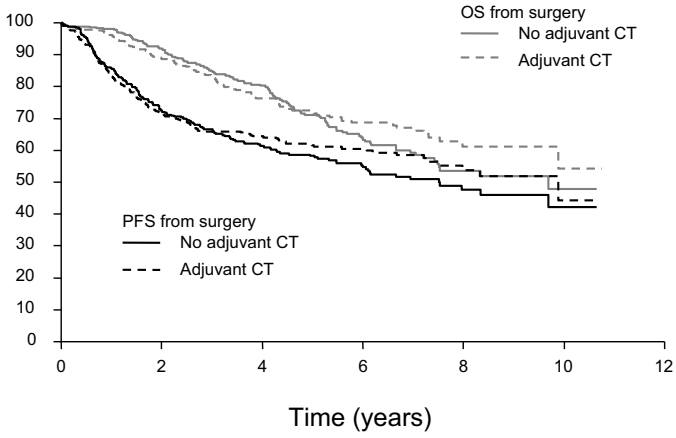
The patients and the potential predictors considered in the analysis are described in Table 1. Because only 5.2% of the cases had mucinous tumours, this variable was not analysed. Although the treatments were randomly assigned, some factors were slightly imbalanced between the two adjuvant treatment groups: WHO performance status more than 1 was more frequent in the adjuvant treatment group (32.2% versus 25%), whereas in the no-adjuvant group, treatment downstaging to ypT0-2 was less frequent (51.8% versus 55.8%) and pN+ cases were less common (25.4% versus 29.5%). The imbalances in prognostic factors seemed to average out: The adjuvant treatment HR for DFS

Table 1. Patient, disease and treatment characteristics considered in the analysis and univariate interaction tests (testing for heterogeneity of treatment effect between levels of the tested classifications).

Characteristics	Frequency		Univariate interaction tests			
	No adjuvant CT (*n* = 403)	Adjuvant CT (*n* = 382)	Disease-free survival		Overall Survival	
	n (%)	*n* (%)	*P*	Interaction HR (95% CI)	*P*	Interaction HR (95% CI)
Patient and disease characteristics at study entry						
Age						
Median	62.5	63.2				
Range	23.3-79.6	22.0-78.6				
≤ 60 years	175 (43.4)	161 (42.1)				
> 60 years	228 (56.6)	221 (57.9)	0.983	1.01 (0.64-1.58)	0.989	1.00 (0.58-1.72)
Sex						
Male	295 (73.2)	285 (74.6)				
Female	108 (26.8)	97 (25.4)	0.588	1.16 (0.68-1.97)	0.965	1.01 (0.52-1.98)
Distance between the tumour and the anal verge						
0-5 cm	198 (49.1)	185 (48.4)				
> 5 cm	205 (50.9)	197 (51.6)	0.202	0.75 (0.48-1.17)	0.026	0.54 (0.31-0.93)
Clinical T category						
T3	368 (91.3)	345 (90.3)				
T4	35 (8.7)	37 (9.7)	0.757	0.90 (0.44-1.81)	0.962	1.02 (0.48-2.18)
Preoperative treatment						
RT	199 (49.4)	190 (49.7)				
RT-CT	204 (50.6)	192 (50.3)	0.763*	1.07 (0.69-1.67)	0.482*	1.21 (0.71-2.06)
Worst WHO grade toxicity during preoperative treatment						
0-1	212 (52.6)	197 (51.6)				
≥ 2	178 (44.2)	176 (46.1)	0.764	0.93 (0.59-1.47)	0.879	0.96 (0.56-1.67)
Missing	13 (3.2)	9 (2.4)				
Surgery						
WHO performance status prior to surgery						
0	294 (73.0)	242 (63.4)				
> 0	101 (25.1)	123 (32.2)	0.984	1.01 (0.62-1.63)	0.398	0.78 (0.43-1.39)
Missing	8 (2.0)	17 (4.5)				

Time from end of the preoperative treatment to surgery						
≤ 6 weeks	271 (67.2)	262 (68.6)				
> 6 weeks	132 (32.8)	120 (31.4)	0.398	0.81 (0.50-1.32)	0.283	0.72 (0.39-1.31)
Surgical procedure						
APR	163 (40.4)	149 (39.0)				
AR or other	240 (59.6)	233 (61.0)	0.146	0.72 (0.46-1.12)	0.023	0.54 (0.32-0.92)
Histopathology						
Tumour length						
≤ 30 mm	244 (60.5)	238 (62.3)				
> 30 mm	143 (35.5)	132 (34.6)	0.474	0.85 (0.53-1.34)	0.780	0.92 (0.53-1.60)
Missing	16 (4.0)	12 (3.1)				
WHO differentiation						
Well	174 (43.2)	153 (40.1)				
Poor/moderate	213 (52.9)	205 (53.7)	0.419	0.83 (0.52-1.31)	0.778	0.92 (0.53-1.60)
Missing	16 (4.0)	24 (6.3)				
Histology						
Mucinous	23 (5.7)	18 (4.7)		Not tested		Not tested
Other	380 (94.3)	363 (95.0)				
Missing	0 (0.0)	1 (0.3)				
Pathologic tumour stage						
ypT0-2	225 (55.8)	198 (51.8)				
ypT3-4	176 (43.7)	183 (47.9)	0.008	1.87 (1.18-2.98)	0.024	1.89 (1.09-3.27)
Missing	2 (0.5)	1 (0.3)				
Number of examined lymph nodes						
< 8	188 (46.7)	167 (43.7)				
≥ 8	206 (51.1)	207 (54.2)	0.714	0.92 (0.59-1.44)	0.895	0.96 (0.56-1.66)
Missing	9 (2.2)	8 (2.1)				
Pathologic nodal status						
ypN0	278 (69.0)	281 (73.6)				
ypN+	119 (29.5)	97 (25.4)	0.818	1.06 (0.67-1.66)	0.903	1.04 (0.59-1.80)
Missing	6 (1.5)	4 (1.0)				
Venous, perineural or lymphatic invasion						
No	310 (76.9)	294 (77.0)	0.568	1.15 (0.71-1.88)	0.423	1.28 (0.70-2.32)
Yes	82 (20.3)	80 (20.9)				
Missing	11 (2.7)	8 (2.1)				

HR = hazard ratio; RT = radiotherapy; RT-CT = radiochemotherapy; AR= anterior resection; APR= abdominoperineal resection. *Not stratified for preoperative treatment.



	O	N	Number of patients at risk				
OS							
No adjuvant CT	119	403	332	208	108	41	9
Adjuvant CT	102	382	300	199	110	37	7
PFS							
No adjuvant CT	170	403	264	164	99	37	8
Adjuvant CT	145	382	244	173	101	33	5

Figure 1. Progression-free survival (PFS) and overall survival (OS) from the date of surgery by adjuvant treatment. O = number of events; N = number of patients; CT = chemotherapy.

was very similar with (HR = 0.94; 95% CI 0.73-1.20; *P* = 0.262) or without (HR = 0.92; 95% CI 0.73-1.14; *P* = 0.443) adjustment for the covariates; as was the adjuvant treatment HR for overall survival with (HR = 0.93; 95% CI 0.69-1.25; *P* = 0.623) or without adjustment for the covariates (HR = 0.92; 95% CI 0.70-1.19; *P* = 0.514).

The univariate interaction tests for DFS and overall survival are also presented in Table 1 with the HRs and the CIs. Only the downstaging (ypT0-2 versus ypT3-4) statistically significantly influenced the magnitude of the adjuvant treatment effect (*P* = 0.008, Figure 2), with an interaction HR of 1.87 (95% CI 1.18-2.98) indicating a significantly larger treatment benefit for the group with downstaging. In the group of patients with downstaging to ypT0-2 at the time of surgery, the treatment HR for DFS was 0.64 (95% CI 0.45-0.91) in favour of adjuvant CT (*P* = 0.013); the DFS rate was 65.6% (95% CI 58.3%-72.0%) without CT and 76.7% (95% CI 69.4%-82.5%) with CT (Figure 3). In patients without downstaging, there was no statistically significant benefit of adjuvant CT (HR = 1.18; 95% CI 0.89-1.57; *P* = 0.244). For that group, the 5-year DFS rate was 48.9% without CT (95% CI 40.8%- 56.5%) and 45.1% with adjuvant CT (95% CI 37.3%-52.5%; Figure 3).

For survival, the downstaging also significantly influenced the effect of the adjuvant treatment (heterogeneity test *P* = 0.024, Figure 4), with an interaction HR of 1.89 (95% CI 1.09-3.27; Table 1). In the group with downstaging, adjuvant CT significantly prolonged survival time after surgery (*P* = 0.030; HR=0.64; 95% CI 0.42-0.96), whereas the group without downstaging did not seem to benefit (*P* = 0.337; HR = 1.19; 95% CI 0.84-1.68).

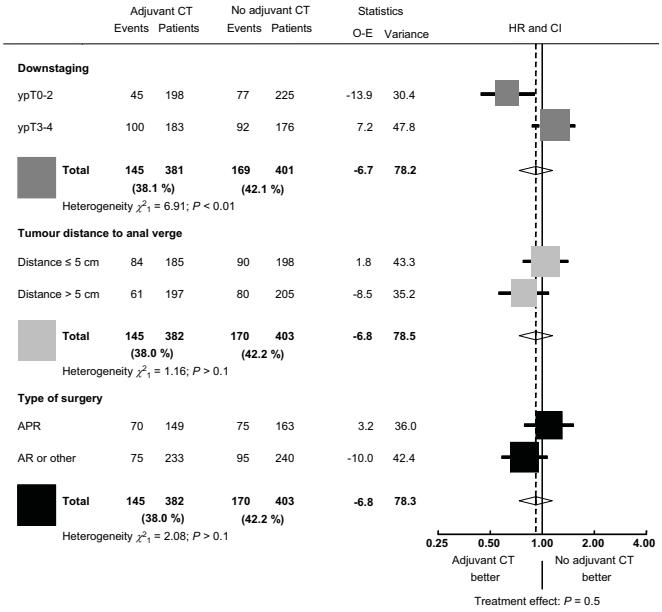
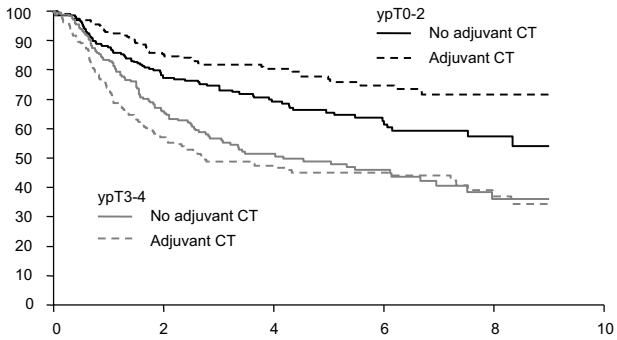


Figure 2. Forest plot of the univariate interactions between the effect of adjuvant chemotherapy (CT) on disease-free survival after surgery and downstaging by preoperative treatment, tumour localisation, and type of surgical procedure. Solid vertical line represents no effect. Dashed vertical line and diamond represent the overall hazard ratio (HR) and confidence interval (CI). Centre of squares indicates HR in each group with 95% CI (horizontal bars). Square size is proportionate to the amount of information in each group. O = number of events observed; E = number of events expected in the absence of treatment effect; APR = abdominoperineal resection; AR = anterior resection.



ypT0-2	O	N	Number of patients at risk			
No adjuvant CT	77	225	157	101	57	22
Adjuvant CT	45	196	150	111	59	16
ypT3-4						
No adjuvant CT	92	176	107	63	42	15
Adjuvant CT	100	183	94	62	42	17

Figure 3. Kaplan-Meier curve of disease-free survival after surgery by adjuvant treatment and pathological down staging to ypT0-2. O = number of events; N = number of patients; CT = chemotherapy.

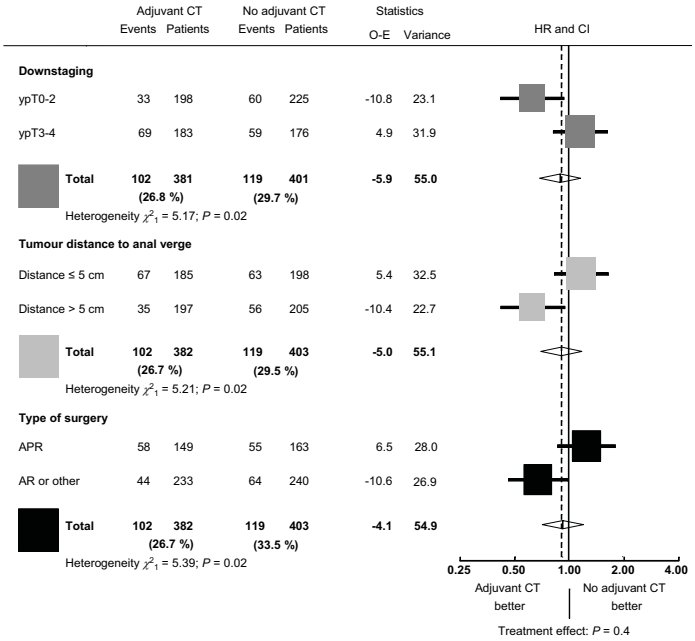


Figure 4. Forest plot of the univariate interactions between the effect of adjuvant chemotherapy (CT) on survival after surgery and downstaging by preoperative treatment, tumour localisation and type of surgical procedure. Solid vertical line represents no effect. Dashed vertical line and diamond represent the overall hazard ratio (HR) and confidence interval (CI). Centre of squares indicates HR in each group with 95% CI (horizontal bars). Square size is proportionate to the amount of information in each group. O = number of events observed; E = number of events expected in the absence of treatment effect; APR = abdominoperineal resection; AR = anterior resection.

Unlike for DFS, the benefit from adjuvant CT was significantly increased in patients with tumour located more than 5 cm from the anal verge compared to the benefit seen in patients with a tumour located at 5 cm from the anal verge (low rectum; heterogeneity test $P = 0.026$; interaction HR = 0.54; 95% CI 0.31-0.98; Figure 4). For tumours in the low rectum, adjuvant CT was not beneficial ($P = 0.353$; HR = 1.18; 95% CI 0.83-1.66), whereas it was beneficial in patients with tumours located higher up in the rectum ($P = 0.033$), with a treatment HR of 0.64 (95% CI 0.42-0.96) indicating prolonged survival with adjuvant treatment. Similarly, the type of surgical procedure also influenced the effect of adjuvant chemotherapy (interaction HR = 0.54; 95% CI 0.31-0.93; $P = 0.026$). Patients who had undergone an abdominoperineal resection (APR) did not seem to benefit from adjuvant CT (HR = 1.26; $P = 0.222$), whereas those with another type of surgical procedure did (HR = 0.68; $P = 0.046$; Figure 4). This is not surprising, because tumour localisation in the rectum is the major driver of choice of the surgical procedure, and 68% of the patients with a tumour in the low rectum underwent APR, compared with only 12% in those with tumours located higher in the rectum.

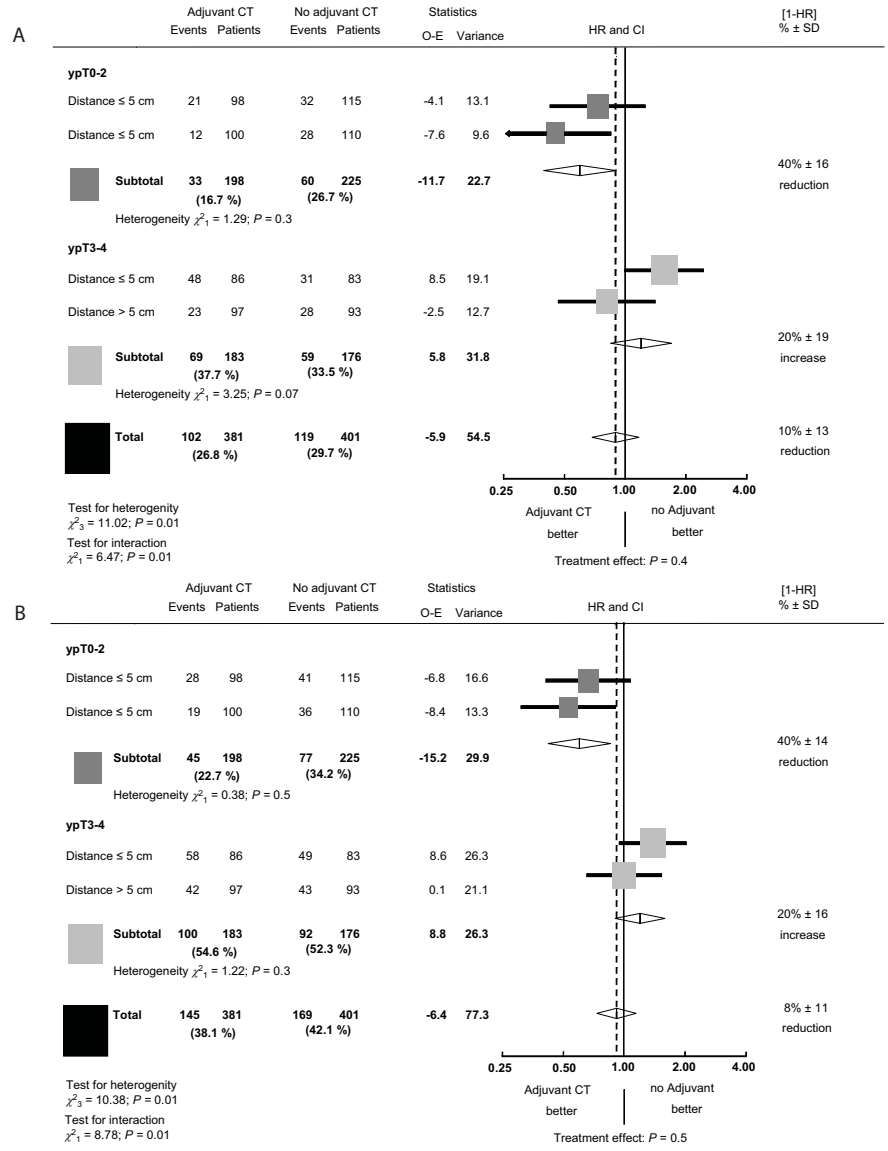


Figure 5. Forest plot of the effect of adjuvant chemotherapy (CT) by downstaging and tumour localisation on (A) overall survival and (B) disease-free survival after surgery. Solid vertical line represents no effect. Dashed vertical line and diamond represent the overall hazard ratio (HR) and confidence interval (CI). Centre of squares indicates HR in each group with 95% CI (horizontal bars). Square size is proportionate to the amount of information in each group. O = number of events observed; E = number of events expected in the absence of treatment effect; SD = standard deviation.

Because the type of surgical procedure and the tumour localisation in the rectum are strongly correlated,[8,9] only the tumour localisation was combined with tumour downstaging for a multivariate predictive factor analysis of overall survival. The four-group

classification combining tumour downstaging (ypT0-2 versus ypT3-4) and tumour localisation (≤ 5 cm versus > 5 cm from the anal verge) statistically significantly influenced the treatment effect (heterogeneity test $P = 0.012$; 3 *df*; Figure 5A). However, within the subgroup with ypT0-2, the treatment effect seemed not to significantly vary according to tumour localisation (heterogeneity $P = 0.255$) whereas it seemed to differ more within the subgroup with ypT3-4, although not statistically significantly (heterogeneity $P = 0.071$). Nevertheless, the three-way interaction amongst ypT, tumour localisation, and treatment was not statistically significant ($P = 0.731$). In the patients with ypT0-2, the HR favoured adjuvant CT (HR = 0.73; 95% CI 0.43-1.26; and HR = 0.45; 95% CI 0.24-0.85 for low and middle/high rectum, respectively). In the patients with ypT3-4 disease, the treatment HRs were not in favour of adjuvant CT: the treatment HR was 1.55, pointing against adjuvant CT for patients with a tumour in the low rectum (95% CI 0.99-2.44; $P = 0.053$), and it was 0.81 for patients with tumours located in the middle or high rectum (95% CI 0.47-1.41).

The impact of this classification on DFS after surgery is represented in Figure 5B and shows that only the classification by ypT influences the treatment effect on this endpoint. The study could not demonstrate a statistically significant behaviour according to the type of preoperative treatment administered, but the predictive effect remained significant even if patients had no preoperatively CT.

DISCUSSION

Overall, the EORTC trial 22921 could not demonstrate that delivering adjuvant CT to all patients with resectable T3-T4 rectal cancer would prolong progression-free or overall survival.[1] In the present analysis, we focused on those patients whose tumour could be resected completely and whose disease had not extended to metastatic sites by the time of the surgery. We then showed that, in the subgroup of patients whose disease had been downstaged to ypT0-2 by preoperative treatment, the delivery of adjuvant CT prolonged both the time to relapse and the survival time.

These findings should not, however, be misinterpreted: It is a common mistake to conclude causality when only associations have been demonstrated. We did not show that it is because tumour downstaging was achieved that these patients also benefited of further CT, but rather that those same patients who achieved downstaging have a disease that is responsive to both the preoperative and the adjuvant treatment. This suggests that the same good prognostic factors induce both an increased likelihood of downstaging from preoperative treatment and increased likelihood of a benefit from adjuvant CT. These findings are no proof of surrogacy of the downstaging for the long-term end-points,[10] but are in line with Valicenti et al.'s statement that heterogene-

ity of tumour behaviour exists, which identification may be promoted by preoperative treatment.[11]

One could then ask which factors drive the sensitivity to pre- and postoperative treatment. In this database, the factors predicting an increased likelihood of downstaging were preoperative treatment,[4] along with tumour length and the use of modern staging by endorectal ultrasonography (data not shown). The factors predicting for progression-free survival after surgery were type of surgical procedure, pN status, microscopic surgical margin status, and tumour downstaging by preoperative treatment.[9] We therefore focused on curatively resected patients. We believe, however, that other factors more closely related to sensitivity to RT and/or CT and to the biology of the disease are probably more relevant to the definition of the "good prognostic" patient group. However, these factors are not known from the data collected in the trial. We can therefore only identify this subgroup a posteriori, on the basis of the pathologic downstaging after preoperative treatment.

The other factors that seemed to influence the effect of the adjuvant treatment on overall survival (tumour localisation and type of surgery) were not confirmed to influence the effect of the treatment on progression-free survival. These factors are known prognostic factors of outcome,[8,9] but in our study, they were not confirmed to be predictive for a benefit from adjuvant treatment regarding progression-free survival.

This analysis is exploratory in nature: neither the end-point nor the hypotheses studied were planned in the study protocol. The hypothesis that a subgroup might benefit from adjuvant treatment emerged from the first trial results that were suggestive of mixture of patients in the sample, with varying sensitivity to and potential benefit from the tested adjuvant treatment. These findings must, therefore, be validated on an independent set of patients with cT3-4 rectal cancer who received preoperative treatment, were operated on, and were downstaged to pT0-2 and are then randomly assigned to receive or not receive fluorouracil-based adjuvant CT.

Despite the lack of evidence to support the routine use of adjuvant CT for all patients with resectable T3-4 rectal cancer after preoperative treatment,[1] adjuvant chemotherapy is regarded by some as standard adjuvant treatment.[12-16] The present report, however, confirms that, at least in patients presenting with poorer risk features (i.e., without tumour downstaging after preoperative radiotherapy or radiochemotherapy), adjuvant chemotherapy with fluorouracil and leucovorin may be an ineffective treatment, causing extra burden and toxicity to the patients without evidence, so far, of any clinical benefit. Our findings contrast with the recommendations by Das et al.[14] who suggest, rather, that adjuvant chemotherapy might benefit more higher-risk patients but are in line with those of Janjan et al.,[17] who report higher rates of relapse despite adjuvant chemotherapy in patients showing no response to preoperative treatment. However, they suggest the use of FOLFOX for high-risk patients, which includes oxali-

platin in addition to the fluorouracil and leucovorin used in EORTC 22921 trial. In a study of 95 rectal cancer patients who all underwent preoperative radiochemotherapy and a microscopically complete resection, Frietkau et al.[13] concluded that postoperative chemotherapy may not be necessary in patients with ypN0. Their conclusions are based on the observation that ypN was the most important and sole independent prognostic factor for disease-free survival in their study and that there was no significant impact of the type, if any, of postoperative treatment on outcome. EORTC 22921 trial confirmed that ypN was a strong independent prognostic factor for overall survival and DFS;[9] however, we demonstrated in the present report that ypN status after preoperative treatment did not show an interaction with the benefit from postoperative CT. The findings reported by Frietkau may well have resulted from lack of power in their analyses, in relation to the limited number of patients in their study.

We can therefore conclude that newer agents are worth investigating either alone or in combination as (neo)adjuvant treatment of rectal cancer, but predictive factors such as tumour responsiveness to preoperative treatment must be taken into account in the design of future phase III trials. Separate treatment strategies may be devised for patients with differing sensitivity to classical chemotherapeutic agents. Finally, the analysis of gene expression profiles of the primary tumour may be relevant to identify patients who may benefit from preoperative radiochemotherapy[16] and adjuvant fluorouracil-based chemotherapy.[18,19]

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